REMARKS/ARGUMENTS

Upon entry of the amendment, claims 7, 9, 13, 15, 19, and 31-44 will be pending in this application and presented for examination. Claims 40-44 are newly added. No new matter has been added. Reconsideration is respectfully requested.

Claims 40-44 are newly added. Support for claims 40-41 is found, for example, on page 9, 3rd paragraph. Support for claims 42-44 is found, for example, on page 11, last paragraph. As such, Applicants request that the Examiner enter the new claims.

I. THE INVENTION

The present invention provides *inter alia*, a mucosal adjuvant for inducing both vaccine antigen-specific antibody in the blood and a vaccine antigen-specific antibody secreted at the mucosal surface. The inventive mucosal adjuvant comprises a natural interferon α as the active ingredient and is administered at the same time as a protein or peptide antigen. When a mucosal adjuvant comprising a natural interferon α and a vaccine antigen comprising a protein or peptide is administered via the nasal mucosal, a systemic immune response is induced as well as a mucosal immune response.

A Declaration by Yuuki Tsutsui is concurrently submitted herein which rebuts any *prima facie* case of obviousness.

II. FIRST REJECTION UNDER 35 U.S.C. § 103(a)

The Examiner has maintained the rejection of claims 7, 9, 13, 15 and 19 under 35 U.S.C. § 103(a) as allegedly being obvious in view of the combination of WO 00/20028 ("Staats *et al.*") and *Kurume Med J., 2001,* Vol. 48, p. 171-174 ("Takasu"). In response, Applicants reepectfully traverse the rejection.

The Examiner states:

> Staats teaches a method of eliciting an immune response by administration of a vaccine antigen and an adjuvant (see abstract, and claim 1). Staats teaches that the vaccine antigen can be either protein

or peptide antigens, including protein peptide antigens from a number of pathogenic organisms (see p. 21, line 11 - p. 23, line 2). Staats also teaches that various cytokines can be used as adjuvants (see p. 14, line 19 - p. 15, line 2, and claims 5-6). Furthermore, Staats teaches mucosal administration of the vaccine adjuvant combination (claim 17), and also teaches that the vaccine-adjuvant induces both systemic (claim 22) and mucosal (claim 25) immune responses. Finally, by teaching that the vaccine and adjuvant are included together as a composition, Staats teach that the vaccine antigen and the adjuvant are administered at the same time and by the same route of administration. However, Staats is silent regarding the use of IFN-a as the adjuvant for any antigen-adjuvant combination or composition.

Takasu teaches that IFN-a is a potent adjuvant for increasing the immune response to various vaccine antigens. Specifically, Takasu discloses that co-administration of IFN-a with influenza virus peptide increased the cytotoxic T lymphocyte (CTL) response to the influenza virus peptide compared to vaccination with the influenza virus peptide alone (see p. 172- 174, Figures 1-3).

A claim is considered obvious "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains" (35 USC § 103(a)). The Supreme Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1395-97 (2007) identified a number of rationales to support a conclusion of obviousness which are consistent with the proper "functional approach" to the determination of obviousness as laid down in *Graham*. The key to supporting any rejection under 35 U.S.C. § 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in *KSR* noted that the analysis supporting a rejection under 35 U.S.C. § 103 should be made explicit. One of the rationales addressed by the court in *KSR* supports a finding of obviousness when the prior art reference (or combination of references) (1) teaches or suggests the claim elements; (2) provides some suggestion or motivation to combine the references; and (3) provides a reasonable expectation of success (MPEP § 2143).

Staats *et al.* provide a laundry list of various cytokines for example, IL-1α, IL-1β, IL-2, IL-5, IL-6, IL-12, IL-15and IL-18; transforming growth factor beta (TGFβ); granulocyte macrophage colony stimulating factor (GM-CSF); and interferon-gamma. These cytokines play a role in the differentiation and growth of T-cell and B-cell directly, and also in antigen-specific inducement of antibodies. In contrast, IFN α is secreted from macrophages and possesses an antivirus effect.

The secondary reference of Takasu teaches away from the present invention. Takasu teaches that the antigen peptide is administered continuously by *osmotic pump*, while the INF-α is *injected* at the site of peptide inoculation. There is absolutely no teaching or suggestion of a nasal administration as is currently claimed, nor is there any teaching of the adjuvant and the peptide being administered at the same time.

Because the route of administration as described in Staats *et al.* is so much different than the use and methods of Takasu, there is no rational underpinning to support a legal conclusion of obviousness. (*KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1396 (U.S. 2007).

As shown in the comparative data filed herewith, and explained more fully below, the antigen-specific IgA excreted from the nasal mucosa confirmed that in the inventive method, IFNα has a higher antibody-inducing ability compared with IFNβ. A high immune response, illustrated by a high IgA titer, was induced on the gastrointestinal mucous membranes by concomitant use of INFα by nasal administration. These results indicate that a systemic immune response as well as a mucosal immune response can be induced by concomitant use of INFα by nasal administration. Accordingly, Applicants respectfully request that the Examiner withdraw the rejection.

III. SECOND REJECTION UNDER 35 U.S.C. § 103(a)

Claims 7, 9, 13, 15, and 19 remain rejected under 35 U.S.C. § 103(a) as allegedly being obvious over U.S. Patent No. 6,436,391 ("Foster *et al.*") in view of U.S. Patent No. 6,361,769 ("Tovey"). In response, Applicants respectfully traverse the rejection.

The Examiner states:

> Foster teaches the use of IFN-a as a vaccine adjuvant to increase B lymphocyte proliferation, and thus increase the effectiveness of vaccines (column 1, lines 52-56), and specifically recites co-administration of a vaccine with IFN-a, or alternatively, a composition comprised of IFN-a and a vaccine (column 1, lines 61-65). Foster is silent regarding mucosal administration of an IFN-a vaccine-adjuvant composition, and is also silent regarding specific amounts or doses of IFN-a.
>
> Tovey teaches a method of stimulating host immunity by oromucosal administration of IFN-a (column 2, line 32 - column 3, line 28). Tovey discloses specific doses of IFN-a that can be oromucosally administered (column 3, line 15-20), and also teaches that IFN-a can be administered as an adjunct to other therapy (column 3, lines 21-22), and specifically mentions previous studies in which IFNs where orally administered to enhance the efficiency of vaccines (column 1, lines 61-66).

Foster *et al.* teach an adjuvant for a vaccine comprising IFN-α_8 and/or IFN-α_{14}. Foster *et al.* do not teach or suggest the administration of natural IFNα with a peptide or protein antigen nasally at the same time. Tovey teaches a method for stimulating the immune response by administering an interferon via oromucosal contact. There is no teaching or suggestion of a mucosal adjuvant comprising a natural interferon α and an antigen comprising a protein or peptide antigen being administered via the nasal mucosal eliciting a systemic immune response as well as a mucosal immune response.

As such, neither Foster *et al.* nor Tovey alone or together teach or suggest the administration of IFNα with the vaccine antigen nasally at the same time to elicit a systemic immune response as well as a mucosal immune response. Nasal administration of a vaccine antigen and an INFα that induces both a vaccine antigen-specific antibody in the blood and a vaccine antigen-specific antibody secreted at the mucosal surface is not taught or suggested in the combination of the cited art.

When a mucosal adjuvant comprising a natural interferon α and a vaccine antigen comprising a protein or peptide is administered via the nasal mucosal a systemic immune response is induced as well as a mucosal immune response. As explained more fully below, the antigen-specific IgA excreted from the nasal mucosa confirmed that in the inventive method, IFNα has a higher antibody-inducing ability compared with IFNβ. The results indicate that a systemic immune response as well as a mucosal immune response can be induced by concomitant use of INFα by nasal administration. Accordingly, Applicants respectfully request that the Examiner withdraw the rejection.

IV. OBJECTIVE EVIDENCE

Applicants can rebut a *prima facie* case of obviousness by presenting comparative test data showing that the claimed invention possesses unexpectedly improved properties or properties that the prior art does not possess. *In re Dillon*, 16 U.S.P.Q. 1897, 1901 (Fed. Cir. 1990). Applicants maintain that a *prima facie* case of obviousness has not been established. However, the comparative data filed in the accompanying declaration rebuts any *prima facie* case of obviousness.

With respect to the rejection of the combination of Staats *et al.* and Takasu, the Examiner states at the top of page 5:

> However, it would be expected, in absence of evidence to the contrary, that a nasally administered composition comprising a vaccine antigen and an IFN-a adjuvant, as is obvious in view of Staats and Takasu, would induce vaccine-antigen specific antibodies at the gastrointestinal mucosal surface and in the blood, wherein said antibodies are IgA and IgG, respectively.

With respect to the rejection over Foster *et al.* and Tovey, the Examiner states at the bottom of page 6:

> Finally, although, neither Foster nor Tovey specifically teach vaccine antigen-specific antibody secreted at the gastrointestinal mucosal surface, wherein said antibody is IgA, or vaccine antigen-specific

> antibody in the blood wherein said antibody is IgG. However, it would be expected, in absence of evidence to the contrary, that a nasally administered composition comprising a vaccine antigen and an IFN-a adjuvant, as is obvious in view of Foster and Tovey, would induce vaccine-antigen specific antibodies at the gastrointestinal mucosal surface and in the blood, wherein said antibodies are IgA and IgG, respectively.

Applicants submit herewith a Declaration of Yuuki Tsutsui, an inventor of the subject application. In the Declaration, a study is described which compares the efficacy of interferon α ("IFNα") as a mucosal adjuvant, against interferon β ("IFNβ") as well as cholera toxin B subunit ("CTB"). The study described herein evaluates the efficacy of IFNα as a mucosal adjuvant compared to IFNβ and CTB. The study shows that the amount of antibody secreted at the mucosal surface is unexpectedly superior in the claimed invention.

As Mr. Tsutsui declares in paragraph 6, IFNα as a mucosal adjuvant was compared to IFNβ using ovalbumin (OVA) as a vaccine antigen. The IFNα or IFNβ at a dose of 4000U along with the OVA was intra-nasally administered to C57BL mice three times at Days 0, 7, and 14.

As Mr. Tsutsui declares in paragraph 7, IFNα as a mucosal adjuvant was tested against CTB, using OVA as a vaccine antigen. The IFNα at a dose of 4000U or 1 μg of CTB along with the OVA was intra-nasally administered to C57BL mice three times at Days 0, 7, and 14.

In paragraph 8 Mr. Tsutsui declares:

> 8. At a dose of 4000U, IFNβ and IFNα, both were confirmed to induce comparable levels of circulating antigen-specific IgG (Fig. 1). On the other hand, examination of the antigen-specific IgA excreted from the nasal mucosa confirmed that IFNα surprisingly has a higher antibody-inducing ability compared with IFNβ (Fig. 2). These results illustrate that IFNα is a cytokine having an unexpected higher mucosal adjuvant efficacy in comparison with IFNβ.

As compared to IFNβ, antigen-specific IgA excreted from the nasal mucosa from IFNα was surprisingly higher compared with IFNβ (Fig. 2). These results illustrate that IFNα is a cytokine having an unexpected higher mucosal adjuvant efficacy in comparison with IFNβ.

In paragraph 9 Mr. Tsutsui declares:

> 9. In addition, IFNα was also compared against CTB, which is a very effective mucosal adjuvant. The dose of CTB applied was 1μg, which has been reported in the literature to exert mucosal adjuvant efficacy. The dose of IFNα applied was 4000U. Both were confirmed to induce comparable levels of circulating antigen-specific IgG (Fig. 3). On the other hand, examination of the antigen-specific IgA excreted from the nasal mucosa confirmed that IFNα has a high antibody-inducing ability. The results illustrate that IFNα has a high mucosal adjuvant efficacy.

Antigen-specific IgA excreted from the nasal mucosa from IFNα was surprisingly high. These results illustrate that IFNα is a cytokine having an unexpected high mucosal adjuvant efficacy.

In paragraph 10 Mr. Tsutsui declares:

> 10 CTB at high doses is widely known to cause adverse effects such as diarrhea, whereas IFNα is applicable at much higher doses in view of known clinical applications. Thus, in application to humans, in is my scientific opinion that IFNα is expected to be useful as a safer and more practical mucosal adjuvant than CTB.

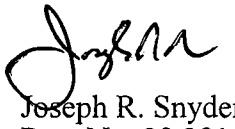
Mr. Tsutsui declares at CTB at high doses is widely known to cause adverse effects such as diarrhea, whereas IFNα is applicable at much higher doses in view of known clinical applications. Thus, it is my scientific opinion that IFNα is expected to be useful as a safer and more practical mucosal adjuvant than CTB. This objective evidence rebuts any *prima facie* case of obviousness. As such, Applicants respectfully request that the Examiner withdraw the rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



Joseph R. Snyder
Reg. No. 39,381

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 925-472-5000
Fax: 415-576-0300
Attachments
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